Systematic review methods for HuGE reviews

Julian Higgins

Public Health Genetics Unit, Cambridge
UK Cochrane Centre, Oxford
MRC Biostatistics Unit, Cambridge

Discussion meeting in Cambridge (UK) Nov 2-3, 2004

- A joint meeting of HuGENet™ and Cambridge Genetics Knowledge Park
- To review and discuss methods for systematic review of gene-disease association studies
  - including gene-gene and gene-environment interactions

Purpose

- To update guidance for HuGE review authors
- To delineate a methodological research agenda

Discussion meeting in Cambridge (UK) Nov 2-3, 2004

Topics

- Study designs and bias
- Identifying studies
- Gene-gene and gene-environment interaction
- Meta-analysis, including
  - Hardy-Weinberg
  - Haplotypes
  - Individual participant data
- Interpretation
  - Reporting biases
  - Observational studies
  - Biomarkers and causality

Fields represented

- Epidemiology
- Human genetics
- Biostatistics
- Public health
- Systematic reviewing
- Information science / librarianship
- UK Biobank
- HuGENet™
- The Cochrane Collaboration

Key outcomes of workshop

To make HuGE reviews…

- more systematic
  - following methods of The Cochrane Collaboration
- more comprehensive
  - thorough searches for studies
  - continued incorporation of joint effects and biomarkers, where possible and relevant
  - increased awareness of risk of bias (within and among studies)
- more quantitative
  - encouraging meta-analysis
  - based on cross-tabulation of outcome by genotype

Continuum of types of review

Systematic reviews of the literature

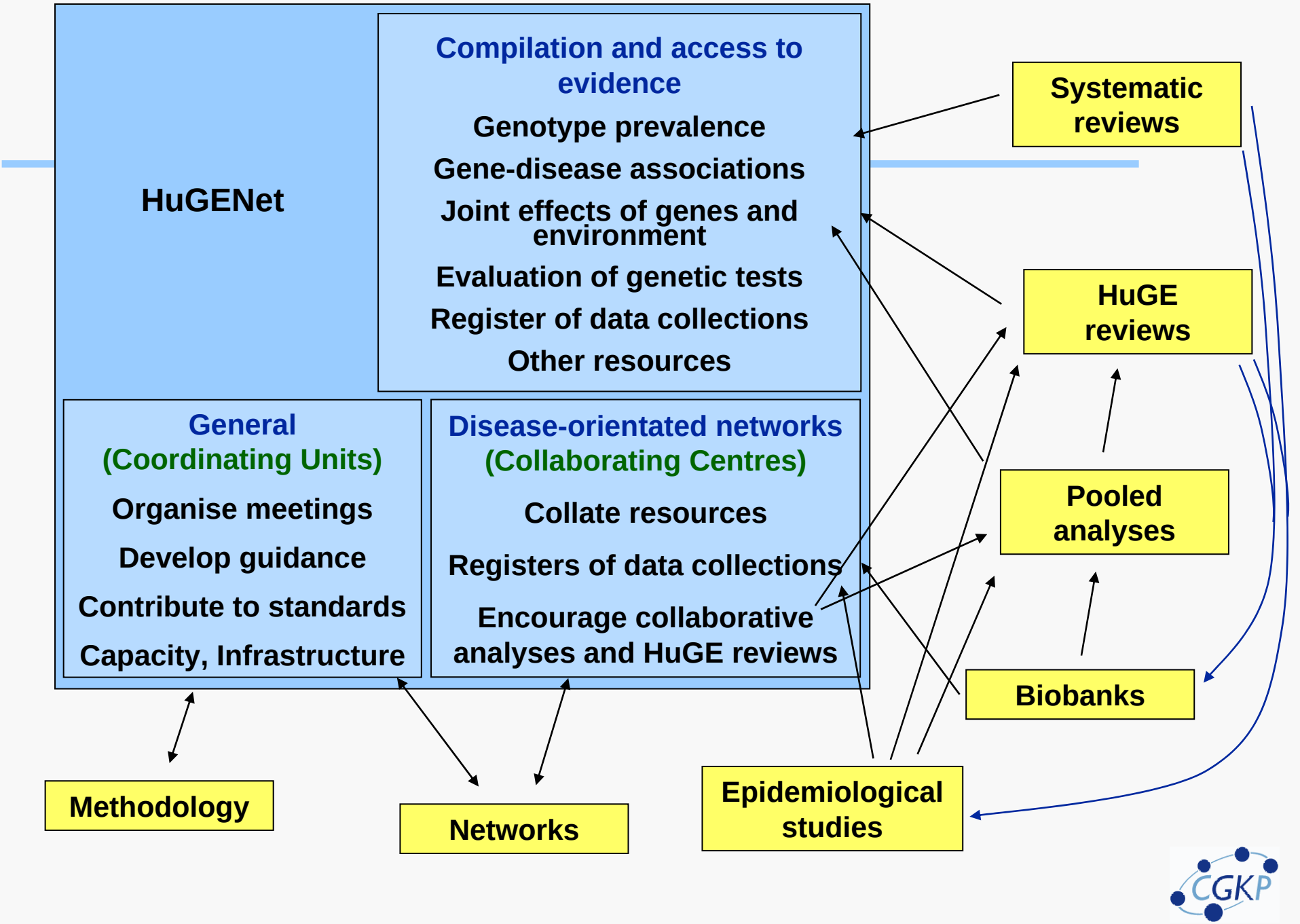
- Majority of existing HuGE reviews

Pooled analyses

- Some existing HuGE reviews
- Initial focus of HuGE networks

Automated syntheses of epidemiological findings

- The (long term) future?
- Requires consistent, agreed format for on-line publication of results


HuGENet
Compilation and access to evidence
Genotype prevalence
Gene-disease associations
Joint effects of genes and environment
Evaluation of genetic tests
Register of data collections
Other resources
General (Coordinating Units)
Organise meetings
Develop guidance
Contribute to standards
Capacity, Infrastructure
Disease-orientated networks (Collaborating Centres)
Collate resources
Registers of data collections
Encourage collaborative analyses and HuGE reviews
Systematic reviews
HuGE reviews
Pooled analyses
Biobanks
Epidemiological studies
Methodology
Networks

Bias in individual studies

- **Variable susceptibility to bias (and information to assess it) - a problem in literature-based reviews**
  - **STROBE statement should help**
  - **Extension of STROBE with specific issues in gene-disease association identified as highly desirable**
- **No consensus on whether to restrict reviews to ‘large’ studies**
- **Typically very little information on which to judge accuracy of genotyping (‘analytic validity’)**
  - **Studies should report genotyping errors**

Gene-gene and gene-environment interaction

- **Fundamental to understanding aetiology and for public health**
- **Very limited (likely misleading) when studies are not large**
  - **false-positive findings likely, and easy post hoc explainations**
- **Desire full cross-tabulations of data**
  - **typically only reasonable in pooled analyses, or with close collaboration of investigators**
- **Large-scale biobank studies have a key role to play here**

Meta-analysis vs single studies

- Debate in the clinical trials field over relative merits of mega-trials vs meta-analysis of small trials
- Meta-analyses provide information on variation in effects across populations, and on using different methods
- But beware reporting biases
- Should large-scale biobanks dwarf findings from smaller studies?
- HuGE reviews / meta-analyses should be used to inform studies on biobank data